UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,010	03/06/2006	Elizabeth Ann Webb	2349.0010000/JUK/MEK	2794

26111 7590 07/24/2008
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
07/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,010	WEBB ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *25 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,5-9 and 12-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,5 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/15/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1, 5-9, 12-30 are pending.

2. Response to restriction requirement filed 04/25/2008 is acknowledged. Applicant elected, with traverse, Group I, claims 1,5,6. Applicant argues that Examiner acknowledges in the restriction requirement that claims in Group I satisfies the unity of invention requirement. First, presence of unity of invention within claims of the same Group is not at issue. Rather, the issue is whether the unity of invention is present between the Groups of inventions identified in the restriction requirement. With this respect, the restriction requirement states that Group I is not the contribution over the prior art because it is suggested by references teaching methods of modifying polypeptide structure to generate candidate polypeptide with reduced amplitude in hydrophobicity or length of a hydrophobic region. Therefore, the lack of unity is present because the linking technical feature is not a "special technical feature" as defined by PCT Rule 13.2. Applicant provided no arguments to traverse the latter conclusion; therefore the restriction requirement is still deemed proper and is therefore made FINAL. Claims 7-9, 12-30 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected groups.

Priority

3. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy of Australian application 200295018 has been filed.

Information Disclosure Statement

4. Applicants' Information Disclosure Statement filed 09/15/2006 has been received and entered into the application. Accordingly, as reflected by the attached completed copies of forms PTO-1449, the cited references have been considered.

Claim Rejections - 35 U.S.C. § 101/ 112-1

The following is a quotation of the 35 U.S.C. § 101:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The pending claims have been reviewed in light of the Utility Examination Guidelines and Guidelines for Examination of Patent Applications under 35 U.S.C. 112,

first paragraph, "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1092-1111, Friday, January 5, 2001.

The examiner is using the following definitions in evaluating the claims for utility.
"Specific" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention.
"Substantial" - A utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. The following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.
B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. § 101.)
C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".
D. A method of making a material that itself has no specific, substantial, and credible utility.
E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

"Credible" - Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record that is probative of the applicant's assertions. That is, the assertion is an inherently unbelievable undertaking or involves implausible scientific principles.
"Well-established" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art.

6. Claims 1, 5, 6 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. The claims are drawn to method f designing a polypeptide having a "reduced amplitude in hydrophobicity" or reduced length of a hydrophobic region compared to original polypeptide of interest. The polypeptide of interest has no identified functional activity and can be a theoretical or non-natural polypeptide of unknown activity. The relationship between the sequence of a peptide and its tertiary structure (i.e., its activity) are not well understood and are not easily predictable. Thus,

changing or rearranging unspecified fractions of protein structure would be expected to cause unpredictable alterations in protein structure and./or function and result in a product having no immediately recognizable utility. Furthermore polypeptide's core residues – which , in most cases, are hydrophobic residues – define the three-dimensional structure of the polypeptide. See, for example, Bowie et al,, p. 1307, first full paragraph; Lim et al, Abstract, last paragraph. Thus, again changing or rearranging unspecified fractions of protein structure would be expected to cause unpredictable alterations in protein structure. To identify a potential utility of thus obtained product would require further research which indicates lack of substantial utility of the instant method. Utilities that require carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utility. The specification does not relate to any "real world" substantial utility of products obtained by the instant method. A method of making a claimed product which itself has no specific, substantial and credible utility does not satisfy utility requirement. See also the MPEP at §§ 2107 - 2107.02

7. Claims 1, 5, 6 are also rejected under 35 U.S.C. §112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1,5,6 may be viewed either as *in vitro* or *in silico* method. To the extent the claimed invention reads on an *in silico* computational method, the following rejection applies.

Claims 1,5,6 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1, 5,6 are drawn to a process and/or system and/or computer software product or computer readable medium. A statutory process or a system or a computer program product that embodies a statutory process must include a final resulting step of a physical transformation, or produce a useful, concrete, and tangible result (State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998), AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999)). Furthermore, a system w/out any physical limitations, which recites only "instructions" type of limitations encompasses a program, per se. A program, per se, is not statutory subject matter. The instant claims do not result in a physical transformation, thus the

Examiner must determine if the instant claims include a useful, concrete, and tangible result.

As noted in State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998) below, the statutory category of the claimed subject matter is not relevant to a determination of whether the claimed subject matter produces a useful, concrete, and tangible result:

> The question of whether a claim encompasses statutory subject matter should not focus on *which* of the four categories of subject matter a claim is directed to 9,-- process, machine, manufacture, or composition of matter--but rather on the essential characteristics of the subject matter, in particular, its practical utility. Section 101 specifies that statutory subject matter must also satisfy the other "conditions and requirements" of Title 35, including novelty, nonobviousness, and adequacy of disclosure and notice. *See In re Warmerdam*, 33 F.3d 1354, 1359, 31 USPQ2d 1754, 1757-58 (Fed. Cir. 1994). For purpose of our analysis, as noted above, claim 1 is directed to a machine programmed with the Hub and Spoke software and admittedly produces a "useful, concrete, and tangible result." *Alappat*, 33 F.3d at 1544, 31 USPQ2d at 1557. This renders it statutory subject matter, even if the useful result is expressed in numbers, such as price, profit, percentage, cost, or loss.

In determining if the claimed subject matter produces a useful, concrete, and tangible result, the Examiner must determine each standard individually. For a claim to be "useful," the claim must produce a result that is specific, and substantial. For a claim to be "concrete," the process must have a result that is reproducible. For a claim to be "tangible," the process must produce a real world result. Furthermore, the claim must be limited only to statutory embodiments.

Claims 1, 5,6 do not produce a tangible result. A tangible result requires that the claims must set forth a practical application to produce a real-world result. In the instant claims such as claim 1, the final method step states the objective "to generate" candidate polypeptide; however, such "generation" is not output in the form immediately

available to a user (e.g., onto a display). It is unclear as to what is done with the resulting data of the final method step. This rejection could be overcome by amendment of the claims to recite that a result of the method is outputted to a display or to a user, or by including a final resulting step of a physical transformation, if such wording is supported by the instant specification.

Further, for an invention to be "useful" it must satisfy the utility requirement of section 101, i.e., it has to be (i) specific, (ii) substantial and (iii) credible. As discussed in the utility rejection above, the invention does not satisfy the criteria of utility requirements as not having a substantial utility.

Therefore, the claims are rejected as non-statutory for failing to comply with 35 USC 101, i.e., not providing a useful, concrete and tangible result.

Claim Rejections - 35 USC § 102 and 103.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. Claims 1, 6 are rejected under 35 U.S.C. 102(a) as anticipated by Tsitrin et al (Tsitrin et al. Nature. Structural Biology, October 2002, vol. 9(10), 729-73), or under 35 U.S.C. 102(b) as anticipated by Keck et al. (US 6273598)

The instant claims are drawn to method for designing a polypeptide comprising identifying one or more hydrophobic peptide sequences within a polypeptide of interest, and arranging or re-locating at least one of said hydrophobic peptide sequences within said polypeptide.

Tsitrin et al. teach conversion of a transmembrane protein (i.e., protein having multiple hydrophobic sequences) to a water-soluble protein by a single point mutation. The conversion is made both in vitro and in silico - in the latter case representation of the results of the mutation are output on the computer (see Fig 3, for example). Note, also that the instant claims do not require mutating to be done *in* silico. The authors identified residues in transmembrane pore of the protein and residue 221 in it located in a subunit interface. Replacement of this residue with glycine has converted transmembrane structure into a soluble protein without loss of its activity or three-dimensional structure. Thus, arranging of one of hydrophobic sequences of polypeptide resulted in generating a polypeptide with reduced amplitude in hydrophobicity (or length of a hydrophobic region).

Keck et al teaches computational methods of producing analogs of morphogenic proteins. Morphogenic proteins are membrane proteins (see col. 3, lines 11-13, for example), i.e., proteins having multiple hydrophobic sequences. The method comprises steps of *in silico* analyzing representation of the protein and modifying it so that to

confer better features, such as solubility or stability. The effect of the amino acid replacements on the solution electrostatic potentials surrounding the modified hOP-1 dimer as well as the free energy of the dimer can be calculated using the available programs. Residues to be replaced can be identified using know computer algorithms (col. 19, 22). Preferred amino acid substitutions lower the free energy of the hOP-1 dimer without introducing potential antigenic sites and without effecting receptor binding domain (i.e., retaining the function). Col. 22, lines 22-43. Thus, once solvent accessible hydrophobic or non-polar amino acids have been identified (see FIG. 9), these amino acids may be computationally replaced with more polar amino acids, thus generating a polypeptide with reduced amplitude in hydrophobicity (or length of a hydrophobic region). The polypeptide analogs are further prepared by methods known in the art and analyzed for activity (col. 26-32).

It is the Examiners position that all the elements of Applicant's invention with respect to the specified claims are instantly disclosed by the teaching of the references cited above.

With respect to claim 6, any polypeptide is considered to comprise a plurality of epitopes.

10. Claims 1,5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsitrin et al (Tsitrin et al. Nature. Structural Biology, October 2002, vol. 9(10), 729-73) or Keck et al. (US 6273598).

The particular embodiment of claim 5 is directed to such polypeptides which are either "non-natural" or "theoretical". Although Tsitrin or Kerk do not teach modifying "non-natural" or "theoretical" proteins" – the results of both methods demonstrate that mutating hydrophobic residues might result in conversion of a membrane-embedded protein into more soluble protein which suggests that upon finding suitable hydrophobic residues other proteins, modifying "non-natural" or "theoretical" proteins included, can be similarly modified.

11. Claims 1,5,6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Benzien (US 20030130827) alone or in view of Tsitrin et al., and Keck et al.

The instant claims are drawn to method for designing a polypeptide comprising identifying one or more hydrophobic peptide sequences within a polypeptide of interest, and arranging or re-locating at least one of said hydrophobic peptide sequences within said polypeptide.

Bentzien et al. is directed to computational method for protein design automation to generate computationally prescreened variants of proteins. The protein of interest can be any protein, such as helical protein having transmembrane helices (paragraph 150), i.e., protein having multiple hydrophobic sequences. Then, the residues to be modified, "variable residues", are identified. Variable residues can be, for example, core residues (paragraph 58) which generally will be selected from the set of hydrophobic residues (paragraph [126]). Algorithms to search for optimum amino acid residue side chain replacements which will produce low energy conformations are used (paragraphs

63, 67, 74, 206) and mutated protein sequences thus identified are output, which resulted in generating a polypeptide with reduced amplitude in hydrophobicity (or length of a hydrophobic region).

The objective of the proteins design automation method of Bentzien is to obtain proteins with optimized structure and desired properties. The desired property can be, for example, solubility of the protein (paragraphs 82, 204, 236, 533).

While addressing all of the limitations of the instant method in general, Bentzien et al. is not directed, specifically, to generating a polypeptide with reduced amplitude in hydrophobicity (or length of a hydrophobic region). However, as Bentzien states that the desired property can be solubility of the protein (paragraphs 82, 204, 236, 533), and that "core residues" of interest are residues of hydrophobic sequences that would be in contact with apolar regions of membrane (paragraph [126]) it would be obvious to one skilled in the art to modify, i.e., arrange, residues of hydrophobic sequences of a protein of interest.

Further, one skilled in the art would have sufficient expectation of success in applying computational design method for *in* silico water solubilizing of a transmembrane protein because the same computational approach was successfully used for water solubilizing other proteins, as described in the references of Tsitrin or Lazar or Kerk .

Thus, Tsitrin et al (reference used in previous art rejection under 35 U.S.C. 102(a)) teach that mutating a hydrophobic residue in a transmembrane protein aerolysin converts it into a water soluble protein.

Thus, Keck et al (reference used in previous art rejection under 35 U.S.C. 102(b)) teach design proteins with lesser degree of hydrophobicity from morphogenic membrane proteins.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Borin, Ph.D./
Primary Examiner, Art Unit 1631